REMARKS

Status of the claims

Claims 8 and 18-19 are pending in the application, with claim 8 being amended and claims 19-22 being newly added. Claim 8 has been amended and new independent claim 19 has been added to separately recite that the Fas antagonist that interacts with the extracellular domain of the Fas ligand is either an anti-Fas ligand antibody (claim 8) or a Fas extracellular domain or a derivative thereof (claim 19). The scope of the subject matter of these respective embodiments has not been changed with these amendments. As such, entry and consideration thereof are respectfully requested.

Rejections under 35 U.S.C.§103

Claim 8 - The rejection under 35 U.S.C.§103 of claim 8 as being obvious over Barr et al., combined with Palmer et al., Du et al., Braun et al., or Baker et al. has been maintained. In addition, the rejection of claim 8 as being obvious over Lynch et al. combined with Palmer et al., Du et al., Braun et al., or Baker et al. has been maintained.

In the Final Office Action, the Examiner does not provide detailed comments as to why the amendments and arguments were insufficient beyond stating that the arguments "have been fully considered but are not deemed persuasive, because the claimed method of treatment remain obvious over the reference teachings." Applicants note that while the Examiner may rely upon previously stated rejections, any final rejection of the claims, "should include a rebuttal of any arguments raised in the applicant's reply." M.P.E.P.§706.07. The Examiner has failed to address

Applicant's previously submitted arguments. As such, it is procedurally improper for the Examiner to finally reject the claims.

In addition, the following comments are submitted to further demonstrate the unobviousness of the instant invention over the prior art.

The method of independent claims 8 and 19 are respectively drawn to methods of treating GVHD with either an anti-Fas ligand antibody or Fas extracellular domain or derivative thereof that interacts with the extracellular domain of the Fas ligand. With the method of the invention, the anti-Fas ligand antibody or Fas extracellular domain interact with the Fas ligand extracellular domain to act upon the Fas pathway and thus inhibit apoptosis, thereby treating GVHD.

The Examiner asserts that "it would also have been prima facie obvious to the person of ordinary skill in the art at the time the invention was made to use the antibodies in a method of treating GVHD, since Palmer, Du, Braun and Baker teach or suggest that the Fas pathway is at least partly responsible for some of the effects in GVHD" (See page 6 of the Office Action).

However, the Examiner oversimplifies the Fas pathway and the corresponding analysis of the instant invention. The Fas/Fas ligand pathway is very complicated and at the time of the invention (i.e. at the priority date of the instant application) many of the specific effects of the Fas pathway were unknown. Even though it was known that the Fas pathway may be at least partially responsible for some of the effects in GVHD, the specific solution that would be effective in the treatment of GVHD remained unknown, e.g. whether apoptosis should be

inhibited and if so at which point in the Fas pathway and in what way, or alternatively, whether apoptosis should be induced and, again, if so, at which point in the Fas pathway and in what way.

The prior art failed to actually demonstrate a prophylactic or therapeutic effect in graft versus host disease (GVHD) by either an anti-Fas ligand antibody or Fas extracellular domain. The present invention represents the first confirmation that an anti-Fas ligand antibody or Fas extracellular domain actually exhibit a prophylactic or therapeutic effect in GVHD (Fig. 15 and Fig 19 of the specification show the increase in the survival rates after transplantation).

Applicants previously submitted WO '627 as evidence that the Fas pathway is very complicated and that many of its specific actions were unknown at the time of the invention. WO '627 discloses the treatment of GVHD by generating Fas/Fas ligand apoptosis. The Examiner newly relies upon Bellgrau et al. (this reference will be discussed in greater detail below) as teaching anti-Fas ligand antibodies (col. 9, line 1 and col. 12, lines 40-45). However in Bellgrau et al. there is no teaching of a humanized anti-Fas ligand antibody. More importantly, there is no teaching in Bellgrau et al. of a method of treating GVDH. Rather, Bellgrau et al. teach the inhibition of T-lymphcyte-mediated rejection by inducing Fas/Fas ligand apoptosis, similarly to WO '627. (See Example 1 of Bellgrau et al. which teaches the inhibition of T-lymphcyte-mediated rejection with transplanted tissues by the administration of Fas ligand.)

Thus, even if a plurality of references recite inhibiting GVHD by generating Fas/Fas ligand apoptosis, as shown above, it was not known at the time of the invention whether a prophylactic or therapeutic effect would be seen in GVHD by inhibiting Fas/Fas ligand apoptosis. Still more, it was not know whether an anti-Fas ligand antibody or Fas extracellular

domain would exhibit prophylactic or therapeutic effect in GVHD. Even if "Palmer, Du, Braun and Baker teach or suggest that the Fas pathway maybe at least partly responsible for some of the effects in GVHD", it would not be obvious for those skilled in the art to use anti-FasL antibody or Fas extracellular domain in the treatment of GVHD.

Palmer, Du, Braun and Baker, who the Examiner rely on to "teach that the Fas pathway is at least partly responsible for some of the effects in GVHD", do not suggest that "using the anti-FasL antibody and the Fas extracellular domain acts upon the FasL extracellular domain to inhibit Fas/FasL apoptosis." Each of the secondary references of Palmer et al., Du et al., Braun et al., and Baker et al. and the unobviousness of the instant invention when combined with primary references will be addressed in turn.

With the primary reference of Barr et al., the Fas ΔTM is a soluble Fas derivative made from an intracellular domain and an extracellular domain. The recited pharmacological action of the Fas ΔTM of Barr et al. is shown by the existence of Fas ΔTM, i.e. intracellular domain and extracellular domain. There is no disclosure in the reference as to whether the same pharmacological action would be exhibited if only one of the domains was present. On the other hand, the active component for the treatment of GVHD of the present invention, is either an anti-Fas ligand antibody or a Fas extracellular domain or a derivative.

With the alternative primary reference of Lynch et al., this reference discloses anti-Fas monoclonal antibody and humanized antibody, and the function of Fas antagonist, but the reference has no recitation concerning GVHD, and there is no suggestion whether an inhibitory effect of Fas ligand alone would be effective for treating GVHD. Lynch et al. is not relevant to

the instant invention because there is no disclosure in Lynch et al. regarding the pharmacological action of the soluble extracellular domain of Fas and anti-Fas ligand antibody.

Thus, as neither Barr et al. nor Lynch et al. have any disclosure concerning the pharmacological action of anti-Fas ligand antibody alone or the Fas extracellular domain the instant invention is not suggested by Barr et al. or Lynch et al. either alone or when combined the secondary references discussed below.

a) US 5776718, Palmer - Palmer mentions that "using ICE inhibitors for GVHD is recited, and apoptosis and cell death are associated with ICE and ICE-like activities and may be treated with the inhibitors". However, there is no suggestion in Palmer concerning the relationship between the ICE inhibitor and the Fas ligand extracellular domain.

The ICE inhibitor recited in Palmer is a material, which inhibits intracellular signal of a Fas-mediated apoptosis. With the present invention, on the other hand, the active component relating to the treatment of GVHD is anti-Fas ligand antibody or a derivative of the Fas extracellular domain. Thus, even if Palmer is combined with Barr et al., it would not be obvious from the combined references that the active component of the present invention, i.e. anti-Fas ligand antibody or Fas extracellular domain can be used for the treatment of GVHD.

In addition, WO '627, which is briefly discussed above, shows that graft transplantation into a Fas ligand genetically deficient mouse, which is non-functional with regard to Fas ligand, has a high transplantation rejection rate (Table l). WO '627 further discloses a method of inhibiting transplantation rejection by administering Fas ligand, and teaches treating GVHD by generating Fas/Fas ligand apoptosis. From a consideration of the teachings of WO '627 it is

clear that Barr et al. and Palmer cannot be combined to achieve the instant invention without the improper use of hindsight reconstruction.

b) *BBRC, vol. 226, pgs. 595 to 600, 1996, Du et al.* - The targets of the Hammerhead ribozyme which are discussed in this reference are Fas ligand and perforin. However, there is no suggestion in the reference as to whether the target exhibiting inhibitory effect with Fas ligand would be effective for GVHD.

As noted above, the target of the Hammerhead ribozyme recited in Du et al. are Fas ligand and perforin and there is no suggestion in Du et al. as to whether there will be any effect on GVHD when the target is Fas ligand alone. In addition, the target in Du et al. is at the genetic level. There is no suggestion nor can it be predicted whether an inhibitory effect on already existing Fas ligand would be effective for treating GVHD. The active component of the method of the present invention may be a Fas extracellular domain by itself. Therefore, even if Du et al. is combined with Barr et al., it would not be obvious from the combination of the references that the active component of the present invention, which is a Fas extracellular domain or derivative thereof or an anti-Fas ligand antibody can be used for the treatment of GVHD.

In addition, as discussed above, WO '627, shows that graft transplantation into a Fas ligand genetically deficient mouse, which is non-functional with regard to Fas ligand, has a high transplantation rejection rate (Table l). WO '627 further discloses a method of inhibiting transplantation rejection by administering Fas ligand, and teaches treating GVHD by generating Fas/Fas ligand apoptosis. From a consideration of the teachings of WO '627 it is clear that Barr

et al. and Du et al. cannot be combined to achieve the instant invention without the improper use of hindsight reconstruction.

c) Journal of Experimental Medicine, vol.183, p. 657-661,1996, Braun et al. - Braun et al. recites that Fas ligand deficient mice have a delay in the onset of GVHD and that the apoptosis relates to GVHD. However, Braun et al. teach that this is also the case with perforin, and that with the donor, GVHD is prevented only when both Fas ligand and perforin become deficient (Fig. 4a), and with the recipient, Braun et al. state that perforin is the essential element (Fig. 4b) . There is no suggestion in Braun et al. as to whether having an inhibitory effect of Fas ligand alone, let alone a Fas ligand extracellular domain specifically, would be effective for treating GVHD.

The active component relating to the treatment method of the present invention is a Fas extracellular domain by itself or an anti-Fas antibody. Thus, even if Braun et al. is combined with Barr et al., it would not be obvious from such a combination that a the Fas extracellular domain by itself can be used for the treatment of GVHD.

In addition, as noted above with regard to Palmer et al. and Du et al. WO '627, shows that graft transplantation to a Fas ligand genetically deficient mouse, which is non-functional with regard to Fas ligand, has a high transplantation rejection rate (Table l). WO '627 further discloses a method of inhibiting transplantation rejection by administering Fas ligand, and teaches treating GVHD by generating Fas/Fas ligand apoptosis.

Finally, the previously submitted reference "Japanese Journal of Transplantation", extra edition, p.180, indicates that in a test using mice, respectively with/without Fas ligand as a donor,

and mice, respectively with/without Fas as a recipient, the combination of a donor with Fas ligand and a recipient with Fas has a high survival extension effect. This paper concludes that the inhibition of the rejection is mediated by Fas ligand and Fas, and this article represents a report that indicates a completely opposite result to Braun et al. Thus, it is clear that the understanding of the art was divided at the time of the invention. From a consideration of the teachings of WO '627 and Japanese Journal of Transplantation it is clear that Barr et al. and Braun et al. cannot be combined to achieve the instant invention without the improper use of hindsight reconstruction.

d) Journal of Experimental Medicine, vol.183, June 1996, p. 2645-2656, Becker et al. –

Becker et al. show with the mouse GVHD model that a recipient receiving cells from a Fas ligand deficient mouse had diminished GVHD symptoms, however, Becker et al. concluded that the pathway of both Fas ligand and perforin are important. There is no suggestion in the reference of whether an inhibitory effect in Fas ligand alone, let alone specifically in the Fas ligand extracellular domain, would be effective for treating GVHD.

As with the other secondary references, WO '627, shows that graft transplantation to a Fas ligand genetically deficient mouse, which is non-functional with regard to Fas ligand, has a high transplantation rejection rate (Table l). WO '627 further discloses a method of inhibiting transplantation rejection by administering Fas ligand, and teaches treating GVHD by generating Fas/Fas ligand apoptosis.

In addition, previously submitted reference "Japanese Journal of Transplantation", extra edition, p.180, indicates that in a test using mice, respectively with/without Fas ligand as a donor, and mice, respectively with/without Fas as a recipient, the combination of a donor with Fas ligand and a recipient with Fas has a high survival extension effect. This paper concludes that the inhibition of the rejection is mediated by Fas ligand and Fas, is this article represents a report that indicates a completely opposite result to Braun et al. Thus, it is clear that the understanding of the art was divided at the time of the invention. Thus, as with the other secondary references, from a consideration of the teachings of WO '627 and Japanese Journal of Transplantation it is clear that Barr et al. and Baker et al. cannot be combined to achieve the instant invention without the improper use of hindsight reconstruction.

Thus, even if the secondary references are combined with the primary references, there is no suggestion in the combined references that "using the anti-FasL antibody and the Fas extracellular domain acts upon the FasL extracellular domain to inhibit Fas/FasL apoptosis". As such, the instant invention is not achieved by or obvious over the combined references and withdrawal of the rejection is respectfully requested.

Claim 18 - The Examiner newly rejects claim 18 under 35 U.S.C.§103 as being obvious over the newly cited reference of Bellgrau et al. combined with the secondary references as discussed above. Bellgrau et al. is relied upon for teaching anti-Fas ligand antibodies. The Examiner notes that the reference does not teach either humanized anti-Fas ligand antibodies or treating GVHD.

Bellgrau is directed to the expression of Fas ligand by transfection with a gene, which encodes the Fas ligand, in order to inhibit T-lymphocyte-mediated transplantation rejection. Namely, Bellgrau discloses inhibiting T-lymphocyte mediated transplantation rejection by inducing Fas/Fas ligand apoptosis. This is completely opposite from the present invention, which "inhibits GVHD by inhibiting Fas/FasL apoptosis using Fas extracellular domain or anti-FasL antibody". Thus, it is inappropriate to use Bellgrau as a reference, because it is a completely opposite solution as that of the present invention. In addition, in Bellgrau, the disclosure of an anti-Fas ligand antibody is only to confirm the expression of Fas ligand. Bellgrau has no disclosure of an anti-Fas ligand antibody having a function as a Fas antagonist.

The secondary references have been discussed above. The analysis of the secondary references is equally applicable herein. For the reasons discussed above, the secondary references similarly fail to make of the deficiencies of Bellgrau and the instant invention is not suggested by the combination of Bellgrau with Palmer et al., Du et al., Braun et al., or Baker et al. As such, withdrawal of the rejection is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, Ph.D. (Reg. No. 40,069) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: May 9, 2006

Respectfully submitted,

By _____
MaryAnne Armstrong, Ph.D.
Registration No.: 40,069
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant